

ME/CFS Symposium – May 28, 2024

Barbara McMakin: Good afternoon, everyone. My name is Barbara McMakin, and I'm from the NINDS Office of Neuroscience Communications and Engagement. On behalf of the NIH, I would like to welcome you to this afternoon's call and to thank you for your interest in participating in this discussion with us today. Today's call is being recorded. If you have any objections, please disconnect at this time.

Dr. Walter Koroshetz, Director of NINDS, will introduce the speakers. Following their updates and presentation, we will open up the webinar to your questions. During the Q and A session, if you have a question for our speakers, please select the raise hand button at the bottom of your Zoom screen and we will call on you to unmute. If you are joining us by phone, please dial *9 to raise or lower your hand and *6 to mute and unmute. You can also submit questions using the Q and A box at the bottom of your screen. Now I would like to hand the call over to Dr. Koroshetz.

Dr. Walter Koroshetz: Well, good afternoon and thank you, Barbara. Welcome to today's ME/CFS webinar. There've been a number of recent developments at NIH and the work that we fund around the country in ME/CFS research, and we look forward to sharing some of those with you today.

Dr. Vicky Whittemore from NINDS will present updates on the NIH ME/CFS Research Roadmap. This is work that was taken on by a Working Group of Council. They worked very hard on a number of workshops over the last year and came up with a roadmap for the important areas in ME/CFS research to pursue in the future based on what has been learned in the past. Dr. Whittemore will also provide funding updates and give a summary of the SPARK ME Symposium, which was an event for early career researchers working on ME/CFS, a very important activity to try and bring more really smart people into ME/CFS research. Next, Dr. Joe Breen from NIAID will talk about what's been going on in the ME/CFS Collaborative Research Centers and the Data Management Coordinating Center, and he'll provide a summary of the NIH ME/CFS and Long COVID Research Conference, which was held in December.

We're also excited to have Dr. Avi Nath as our guest speaker this afternoon. Dr. Nath is the Clinical Director for NINDS and the Chief of the Section on Infections of the Nervous System. His research has included the pathogenesis of HIV infection in the nervous system, endogenous retroviruses and undiagnosed neuroimmune and neuro infectious diseases, and for several years now has been investigating ME/CFS and more recently the effect of SARS-CoV-2 on the nervous system and causes of long COVID. Dr. Nath, we're happy to say, was recently named to the 2024 TIME100 Health, a list of 100 individuals who most influenced global health. And he'll be speaking to us this afternoon about his latest research in ME/CFS and potentially Long COVID. So we look forward to hearing from you and, and then answering your questions following the updates and Dr. Nath's presentation. And with that, I'd like to turn the call over to Dr. Vicky Whittemore. Vicky?

Dr. Vicky Whittemore: Thank you, Dr. Koroshetz. Yeah, I'd just like to give you some updates. So the Research Roadmap was presented and approved by the NINDS Advisory Council on May 15th and is posted online for anyone who would like to take a look at the Research Roadmap as well as all of the webinars. We held eight webinars that led up to that Research Roadmap report.

I think what's interesting about the report is that there's sort of two levels of recommendations. So if you look at each of the sections, there's pretty detailed research priorities that came from each of those areas of research, some of them overlapping obviously, but some of them very detailed and specific to that area of research. But I think the important overarching priorities really are, and what was the goal of the research roadmap was to talk about how do we move forward to get to clinical trials.

And so coming out of that planning process and now the report, is we're moving forward with having pretty significant conversations about how to move forward with clinical trials both here in the United States as well as with our international colleagues. And there will be some discussion about that at the upcoming Invest in ME conference that will take place in England, excuse me, in England at the end of June. And in addition, there's some other things that we're working toward, which is to pull together a genetics consortium to bring together all of the data and the advances and the work that's being done across the globe on looking at the genetic susceptibility and genetics of ME/CFS to try to understand what do we know about the heterogeneity and genetic susceptibility of individuals who have ME/CFS and as it compares to individuals who have long COVID, because there's a lot of that work that has now been done with long COVID. So the Trans-NIH MECFS Working Group will be meeting to talk about additional next steps, but we're really trying to tackle some of these big issues while we'll also try to move forward on the current funding and the current grants that we are supporting.

So with regard to grant support, we will be funding an additional Center. It hasn't been announced yet because we're waiting for them to receive IRB approval or approval for their human subject studies, but hopefully that will be coming soon. I know that at NINDS we have two additional grants on ME/CFS that are being, in the process of being reviewed and funded. And there are, I've seen now that there are several applications that have come into NINDS for review in the next cycle. So that's exciting. And I think the good news also is that there's a lot of new investigators coming into the field and a lot of new ideas. So that's always really great to see those grants coming forward.

And lastly, I just want to comment on the SPARK ME/CFS workshop we had at the, I guess, back in December, in conjunction with the NIH conference that Joe Breen will talk about. We had individuals both in person and online again from around the world, from Europe, from Australia and the U.S. who joined us for that. And these were all early career investigators. So graduate students, postdocs, some, actually a high school student, some undergrads, as well as young junior faculty who came together to really talk about their research and what's going on in ME/CFS and to talk about the issues that they face in doing research in ME/CFS and to get advice and support on how to continue their research careers in ME/CFS. And to that end, they've now developed a LinkedIn group, they've developed a journal club where they're continuing to meet to really help provide that support and input from other people who are their peers. We're not involved in that. That's really something that they're taking forward. But it's really again, exciting to see that support and that networking happen between all of these early stage investigators. So with that, I will turn it over to my colleague, Dr. Joseph Breen from NIAID.

Dr. Joseph Breen: Thank you, Vicky. My name is Joe Breen. I'm a program official at NIAID and I work closely with Vicky on ME/CFS across the NIH. And I want to tell you about a few activities. Vicky introduced them.

The two are the Collaborative Research Centers, which at this point is a Center at Cornell led by Maureen Hanson and Andrew Grimson and the Data Management Coordinating Center, which is run by Drs. Megan Carnes and Linda Brown at RTI. And the Cornell Center, which is actually been awarded about a year ago, has actually been quite productive already and their work was definitely present at the research conference held in December that I'm gonna talk about in a moment. And they've published four papers actually in even the last year in areas of transcriptomics, really trying to understand, you know, single cell, really detailed transcriptomics changes in the immune system. That study is led by Andrew Grimson. He actually spoke about it in the December symposium meeting at NIH. And then subsequently, actually the paper was published in *Cell Reports* in January of this year, and the Center at Cornell also published work on some cytokine analysis as well as exosomes. And then a very interesting paper about potential viral origins of ME/CFS, which is still never been quite clear, but Dr. Hanson makes an argument for enteroviruses, which is very compelling reading. And I would encourage you to look at that one in *PLOS Pathogens*, it's a publicly available journal.

The Data Management Coordinating Center is increasingly developing tools to look at the data from the Collaborative Centers that can be applied more broadly. And they have really taken on this mission and have recently brought in the data from Drs. Walitt and Nath's recently published work, which I'm sure you'll hear a little bit about. So that has increased the amount of data in the mapMECFS network and will really help those cross-comparisons which are so vital in a field like this. And they, not only do they develop to curate data that's in there, they are developing tools in really an exceptional manner and then coordinating that, of course, with searchMECFS, a way to get biospecimens as well.

With regards to the research meeting that Vicky mentioned, it was a meeting held at NIH "Advancing ME/CFS Research: Identifying Targets for Intervention and Learning from Long COVID" which was really designed to leverage what we know from the pandemic to ME/CFS research. It was a two-day meeting and this meeting was particularly rich with lived experience, individuals, a number each day speaking to

really provide perspective as to why we really need to understand what's going on at the pathobiology level, and it was very compelling. The other thing I'll say from the meeting, it was really designed in a very similar way as the 2019 meeting, but was much more diverse and rich in data and really I think represents where people are now thinking, people in the field are thinking about pathways for clinical trials and I'll point out a few things that were new at the meeting in that vane.

Dr. Mark Davis from Stanford presented some data that's unpublished to my knowledge, but he presented an elevated reactive oxygen species in female ME/CFS patients and female Long COVID patients. And again, this is a point that was emphasized in several different independent investigative talks, that the sex differences between men and women was very apparent. We've seen immunological differences in men versus women with ME/CFS as well as some age differences. But it's really striking how these are now being found in a very mechanistic level.

And Dr. Davis's work is really pointing, as well as others, to mitochondrial pathways that are different. And there were other talks such as Dr. Derya Unutmaz, who runs a Collaborative Research Center at Jackson Labs funded by NINDS until recently, where he looked at immune system determinants and really uses routinely AI-driven multiomics modeling to try and understand the phenotypes present with ME/CFS. And he noted, as well as Dr. Ian Lipkin's group, the disrupted butyrate and tryptophan pathways. And again, highlighting in his work, Dr. Unutmaz' work, the differences found in gender and sex differences is really helping us understand the biology. Again, the point of that is trying to lead us towards clinical trials, which may end up pointing us towards personalized medicine due to the heterogeneity, which was pointed out by Dr. Lipkin in fact, who has a Collaborative Research Center.

You know, and one point that Dr. Lipkin brought up in the conference was to remind us to look at the innate immune system as well. I think his group and as well as others have looked at adaptive immune differences and there is now evidence for innate immune memory being present in COVID, for example. And Dr. Lipkin was reminding us in the conference that we need to think about the innate immune system differences in ME/CFS as well, trying to stimulate the field to think about that. And I'll skip over Dr. Nath's work because you're gonna hear about some of that.

And at the conference, we also heard about mitochondrial perturbation and some bioenergetic deficiencies by Paul Hwang from the National Heart, Lung, and Blood Institute, whose work was really published just prior to the conference. So it was really an interesting mixture of unpublished and published data, again highlighting some really targetable mechanisms. We don't yet know how generalizable they are, but I think, you know, he looked in ME/CFS patients and did find some of this WASF3 family member protein looking as a potential candidate for a difference in ME/CFS patients. And his data would suggest that it's a variant of autoimmune disease. And Karl Johan Tronstad from Norway also in his talk was highlighting that are variants and aspects of autoimmune disease. Again, I know that's not a new hypothesis in the field, but it's adding to the overall picture and in particular, when we can couple that with some physical differences that are measured, again, that can help point us towards potential targets for intervention.

The day, the second day ended with Dr. Tony Komaroff providing a summary. And I'll end here and just say again that the entire conference is available at the NIH video conferencing site with some annotation for the talks. And I would encourage folks who are interested in specific areas to go and look at that publicly available conference and really see what the state-of-the-art are at the time. Again, six months ago, science moves quickly, and we hope as we saw in this conference, that the field is moving towards better understanding of pathways, trying to find targets for intervention and putting the two together. And I think what we saw was we're much closer today than we were just a few short years ago. And I'll end there. And I believe Dr. Nath is up next. Over.

Dr. Avindra Nath: Thanks, Joe. That was a beautiful summary of the research here. So I'm going to present to you just a few slides. And 10 to 15 minutes can't do justice to a very large study, but this is what I presented at the recent patient symposium, and I've just expanded upon that.

I've titled it "The Tale of Three Pandemics." Okay. And the reason for that is that when I started my career in the 80s, early 80s, when the AIDS pandemic first started, there again, you had patients with all kinds of medical conditions, and we didn't know what was really causing it. And patients were developing neurological complications. And then we later found out, oh, it was a virus that was doing it. So that set off people like myself investigating all these years to understand how the virus can cause neurological damage, and we're still studying it 40 years later.

Then came the Ebola pandemic. And then I got focused on starting to understand how Ebola, that actually causes a GI illness, how that causes neurological complications. And here again, patients were developing meningoencephalitis. And just as we started studying this pandemic, I got involved in the ME/CFS study. So I took on both these studies at approximately the same time, but I'll draw parallels between these. And then comes on the SARS-CoV-2 pandemic and they also are quite similar in the neurological complications. So I think by studying these, you really can understand ME/CFS a lot better than just studying one disease by itself.

And so now with Ebola, what we also found is that patients who recover from the infection go on to develop a condition called post-Ebola syndrome. And so we've been following over 200 patients now in Liberia for several years. And the kinds of symptoms that they develop are quite similar to what patients with ME/CFS experience. So here's an opportunity in a totally different setting. Yeah, totally different virus, but causing symptoms that are somewhat similar. So one can learn from that.

And then I'll talk a little bit about Long COVID. But I think you already know that there are huge amounts of overlap between the two. And when SARS was recognized as a virus causing neurological symptoms, I was very concerned that Long COVID is going to be the consequence. And in fact, some of my very early writings had indicated that we need to be aware that a neurological syndrome similar to ME/CFS is going to emerge in the SARS-CoV-2 infected patients. So here I want to depict that these three syndromes do overlap with one another. And I think most appropriately, instead of giving them separate names, we should call them post-acute infection syndromes. And I think by and large, more and more people are starting to recognize that this probably is a more appropriate term. And then a whole slew of diseases can be put under that umbrella. And that may include, you know, post-Lyme syndrome and Gulf War syndrome, sick building syndrome, and many others.

But what is also fascinating to me is that you've been studying HIV for several decades and here you do have a persistent infection. The viral reservoir remains from the time you're infected. It never goes away. But what is fascinating is that these patients do not develop ME/CFS-like symptoms. So these other infections do, but this one does not. So if persistent viral infection was the only reason for developing these post-acute infection syndromes, that doesn't seem to be the case with HIV.

I think we can learn a lot by studying HIV because now you can compare and contrast and try to see why is it that one set of individuals do and the others do not? When they have similar increase in cytokines they have mitochondrial dysfunction. They have, you know, all the other pathophysiological things that we think are happening in these patients you can find in the HIV patients, but yet they're not developing the same syndrome. So I think we will help dispel some of these hypotheses and maybe allow us to explore new ones.

What is interesting, however, is that if you look at and these syndromes, you know, the ME/CFS, post-Ebola, and Long COVID, the initiating event is either a gastrointestinal or respiratory infection. Okay. And so it tells you that there's something happening at the mucosal surfaces here and maybe there's a defect in the mucosal immunity that could be triggering some of these things. While in HIV, the persistent reservoirs are all in the lymphoid tissues and in brain, right?

So we recently published this paper and this summarizes what we think is probably ongoing in patients with ME/CFS. Again, you know, it's still a hypothesis. We have found a number of abnormalities and we've tried to piece it together to try and see if we can make some sense of it. So accordingly, what we think is happening is that there is an infection that takes place, as I said, it's often a respiratory or intestinal infection, and that can lead to change in the microbiome. It can also cause immune dysfunction, which we think is sex dependent. So just as Joe Breen mentioned, we found that the type of immune responses you get in men and women are somewhat different. But nonetheless, what we find is that there's a failure of the immune system and that failure probably leads to antigen persistence.

Okay, once you have this antigen persistence, you will get immune exhaustion, persistent immune activation. And what that leads to is a dysfunction in the neuroimmune axis. And then you start seeing all kinds of metabolic abnormalities within the central nervous system. On the other hand, as I also mentioned is that the microbial abnormalities here in the intestine can also lead to a leaky gut syndrome or abnormal absorption of things, particularly tryptophan absorption can be decreased.

And so that pathway gets impacted, and it's supposed to form serotonin, and that can affect the brain as well. And this can manifest in your endocrine abnormalities, particularly leading to abnormalities in the autonomic nervous system and also affecting the ability of the brain to really react in many different ways. And that's been localized electrophysiologically to this area called the parietal temporal junction. And eventually this leads to electrophysiological abnormalities and motor output abnormalities resulting in the clinical syndrome of ME/CFS.

So I'm going to focus on the immune abnormalities, which I think there are the early events and that's what's driving the rest of the syndrome. What we found, and I think this is a very novel observation that I think is the initiating event underlying ME/CFS, and that is the inability of B cells to switch to an antibody producing B cell. And this is absolutely critical and is a very early event that occurs when you're faced with any kind of offending microbial antigen. And if one is unable to do that through the germinal center, then what happens is that the T cells have to pass through the germinal center in order to get the antigen has to be presented by the B cells to the T cells, and that's where the T cells go and get rid of the antigen. So the switching doesn't take place. The T cells are never going to get appropriately activated because the antigen has never been presented to them. And what that results in is T cell exhaustion.

Okay, so you get these T cells that are exhausted, so they're unable to really get rid of the antigen. When you have T cell exhaustion, what's going to happen is that the innate immune system, which is your macrophages and others, now they come into play. They say, well, the T cells aren't doing their job of getting rid of this. Maybe the innate immune system should try to do it. And then that's what produces the oxidative stress, all those kinds of cytokines. And I think that's what produces the clinical phenotype of the post-exertional malaise and the like.

And so these are the three key components of the immune system that are dysregulated in these ME/CFS patients. And we found that in Long COVID as well. So here are the patients with Long COVID that we followed here at NIH. And these visits are one year apart, and what I can show you is that this is a marker of immune exhaustion and this is another marker of immune exhaustion. These are the same individuals we followed. This gray box over here suggests where the normal values should be. And you can see that they're elevated in these Long COVID patients, and they stay elevated a year later, right? And the same thing here, you can see majority of these patients here show persistent checkpoint expression in these monocytes here, suggesting that these cells are immune exhausted. So what are the next steps then?

I think from our study we generated a lot of data. We made all of it publicly available. This was a massive undertaking and so it gives us an opportunity to continue to analyze it. We have several other manuscripts in various stages of publication right now. And then plans to reanalyze the data in the context of other research being done by other groups to validate our findings and other cohorts and discuss and develop plans for clinical trials.

I think we have enough data right now on pathophysiology and what we've done so far that it provides us an opportunity to identify these target antigens, therapeutic targets, and initiate clinical trials. I think that's a major outcome of our study is that you can still continue to study pathophysiology, but I would suggest that we do it in the context of clinical trials.

So what can you do for clinical trials? You can attack this pathway at many different levels depending on your area of expertise. I focus primarily on the immune system. That's where my expertise lies. Yeah. However, you know, it's perfectly fine to try and impact these metabolites over here, maybe increase tryptophan uptake if one can possibly do and manipulate the microbiome if you can. But these are things that I call reactionary. These are early enough in the pathway over here you can have an impact. Also, these are largely symptomatic type therapies. The one possibility is that if you were to block it here, you could block the entire cascade, and I think that probably is true if you were to catch patients early in the course of their illness. After a while, what you worry about is that some of these later pathways can actually become self-perpetuating, so then just blocking the early immune pathways alone may not be sufficient. And you may need some kind of combination therapy where you have to combine both these symptomatic treatments as well as something here in the early phases. So what do you hope to achieve from that?

If you can, if you act here in this area of the cascade, then you may be able to either reverse, halt, or at least slow the progression of the disease. And in the latter part, what you can do is at least provide symptomatic treatment to individuals so you can still improve their quality of life quite tremendously. Okay, so what are the potential targets?

So here's a whole list of them. This is the same list that I presented in my previous talk. It looks like some people really didn't quite get it, so I'm presenting it again. So you can target, you know, the two things you should know are, number one is that these should not be used helter-skelter. These things are pretty, you know, powerful agents and they can have pretty profound side effects. So one has to use them very carefully. And so they should be done in the context of clinical trials, but for individuals who have T cell exhaustion. And you could put them in a clinical trial with checkpoint inhibitors. Individuals who have predominantly B cell activation, and these are mainly women, you

have another set of choices here. T cell activation, you have multiple different other choice of drugs here. Innate immune activation, you can block over here. So there are a number of different targets that one can try to impact by using these biological agents. Okay, and there are also non-specific ways of being able to modulate the immune system.

Patients have written to me a number of times suggesting various other types of drugs that they think have helped them in one way or another. And I think those are all reasonable things to also consider in the context of a clinical trial. Now, what should be the trial design?

And so, you know, traditionally we do single drug, placebo-controlled studies. The problem with that is that it could take decades, if not a century, before we go through all these drugs. So I think more and more people have started thinking about platform studies whereby you can test many different drugs at the same time. And so they have their own challenges, but nonetheless, I think for several types of drugs this may actually work really well. So I think that's something we need to think about. And that doesn't mean that there's not a role for single drugs to be tested in a placebo-controlled study. And then there are certain things that are called the crossover studies whereby you know, you could put a person on placebo or drug, but then after a period of time those who got placebo switch to drug and those who got the drug switch to placebo. So that way every participant has the opportunity to at least benefit from the trial.

Okay, so what are we doing right now at NIH in the intramural program? Our current focus is on these Long COVID patients. And so we have a deep phenotyping study pretty similar to what we did for ME/CFS and we want to compare the two to see how much overlap there truly is, and how many, and what the differences might be. And then another study is an interventional study that we are doing with immunoglobulin that's IVIG. And so we've enrolled 14 right now and our goal is to get to 34. And that's a crossover placebo-controlled study, and we're in the process of writing up a protocol on pembrolizumab and that's still in development. At the moment we want to look at tissue reservoirs. So we want to see if there really is persistent antigen, and that is currently in scientific review. And then we want to look at the neuropathology of Long COVID, and that is ongoing.

I think we made significant progress so far studying ME/CFS. But I think further progress is only possible if we have a true partnership with the patients. And I think together, if you can work together, we can really achieve the impossible and we can develop treatments and cures. And I think that is key to this whole process. But if you're hypercritical of the people and the researchers who are trying to help you, then we do get demoralized and you tear us apart. And then it becomes very difficult to achieve the goals that we've set out to achieve. So I'll stop here and take any questions.

Barbara McMakin: Great. Thank you, Dr. Nath for that excellent presentation. We will now transition to the question and answer session. As a reminder, if you have a question for our speakers, please select the raise hand button at the bottom of your Zoom screen and we will call on you to unmute. If you are joining us by phone, please dial *9 to raise or lower your hand and *6 to mute and unmute. You can also submit questions using the Q and A box. We will try to answer as many questions as possible, but we may not be able to get to all of them, and we want to hear from as many people as possible. So we request that everyone ask only one question. And as a reminder, this call is open to the public and is being recorded. So please exercise discretion and sharing personal information, including personal medical information.

We've already received several questions in the Q and A box. Dr. Nath, the first one is for you. I understand there are still a lot of yet to be published data from the deep phenotyping study. Does this include comparisons between patients and controls specifically in the post-exercise period? If not, are there future plans to look more deeply into what exactly is going wrong after exertion or exercise?

Dr. Avindra Nath: Yeah, so you're right. Yeah, we do have data on post exercise and yeah, so we're in the process of putting that together. That will come out in the form of a publication.

Barbara McMakin: Great, thank you. I think this next question is for really any of our panelists. Since ME/CFS can impact any age, what can be done to include cohorts that are under 18 and over 65?

Dr. Vicky Whittemore: I'll take that first if you want. So I think, you know, we've been working with our colleagues at NICHD, the National Institute of Child Health and Human Development, and they are very interested in research on ME/CFS in children and adolescents. We just haven't received those grant applications. But I think, you know, going forward if we're talking about clinical trials, it will be important and

interesting to include those different ends of the age, age range, as well, not just individuals 18 to say 65. Avi, did you want to respond to that?

Dr. Avindra Nath: I couldn't agree with you more. You know, those are challenging studies because you need appropriate sample sizes to really make any heads or tails from it. So you need mass populations and in children that's the problem is that, you know, getting controls is very hard. How can you put in, you know, healthy kids in these very extensive studies, pull them out of school?

So there are practical challenges and these kinds of things, and older individuals, there are a lot of other comorbidities associated with them. And so how do you sort out what is due to this disease and what is to the underlying Alzheimer's or Parkinson's, whatever else they might have hypertension, you know? So these are practical challenges. But yes, if one can, one needs to think about how to do them.

Barbara McMakin: Okay, great, thank you. I have another question that I'll open up to all of our panelists. What would personalized medicine look like in ME/CFS as compared to cancer?

Dr. Joseph Breen: I think I mentioned something that was talked about at the December conference. And maybe Vicky, if I could ask you to talk about the research roadmap and the consortium for genetics? Because I think it might play a role.

Dr. Vicky Whittemore: Yes, so I think the genetics findings that we heard about in the webinar, as well as the different immune profiling and deep phenotyping studies that are coming out looking at metabolism and other -omics, really indicate that there are these different subtypes. And so again, it's something we need to think very carefully about moving forward in terms of identifying study participants for particular clinical trials because it might not make sense, for example, to have someone in a clinical trial that's focused on say, trying to correct any kind of T cell exhaustion if that individual doesn't have T cell exhaustion. So I think these are all going to be really challenging but important things to consider as we go forward. And Avi may want to say something more about the deep phenotyping.

Dr. Avindra Nath: I agree with you. Okay, I mean they really need to do the immune phenotyping in order to try to identify what treatment trial you want to put them in, and eventually what treatment you want to give them. So yes, you're right. Some will have B cell activation, some may have T cell activation, some may have T cell exhaustion. So you want to treat them accordingly and some can have more than one.

Dr. Joseph Breen: Yeah, I guess what I was thinking is that I can see that we might be able to immunophenotype to get buckets where we could expect therapies to differ. It would be different than a cancer, a tumor for example, that's genotyped. But then the treatment depends on the genotype and can be specifically designed for that genotype. I think the buckets, probably the way I see it at least in the intermediate future, is that you could get immune phenotype buckets, whether it's age, immune function, functional tests, like some of the things that you're talking about, that you could take into account in terms of your strategy. I think that's what the short-term personalized approach would probably look like. Would you both agree with that?

Dr. Avindra Nath: Yeah, yeah, absolutely. That makes sense.

Barbara McMakin: Great. Thank you. We do have a couple of attendees with their hands raised. Sonia Irey, apologies if I'm mispronouncing your last name. You can go ahead and unmute your line.

Sonia Irey: Thank you so much. I'm really grateful for the work that you've done on this and I'm very interested to know how you anticipate moving forward with ME/CFS? I know you said that you're working with Long COVID studies, but how do you anticipate moving forward with the ME/CFS clinical trials that you said are so important to advancing the science on this disease?

Dr. Avindra Nath: Yeah, yeah. So, you know, the way I think about it is that pathophysiologically, ME/CFS and Long COVID are similar. I think considering the fact that there are just so many more people now with Long COVID and that we know in Long COVID at least what the initiating event is and it's the same virus for all of them. I think doing those clinical trials would be much more expeditious. And we can come to the answers a lot faster and they can then be applied immediately to ME/CFS. There's no reason to have to re-do any of those things because we would, you know, the phenotyping and other things already overlapping with what we find with Long COVID. So that's the way I'm thinking is, that if we do it and you know, the Long COVID and ME/CFS patients will get the answers a lot faster.

Dr. Vicky Whittemore: But just to add to that, the Neuro clinical trial that's being supported through the RECOVER Initiative is just about completed and will soon complete, their the autonomic clinical trial is ongoing, and the energize clinical trials, and I'm blanking on what the other one is, Joe or Walter might help me. Sleep. So those are going to start to enroll, are due to start enrolling in June. And so those clinical trials, as Avi said, hopefully will give us some pretty important and interesting clues that will help us to understand at least, maybe initially, some of the clinical trials or treatments that we can move forward to ME/CFS.

Dr. Walter Koroshetz: Just to add, I'm sure NIAID, NINDS have open door mechanisms for clinical trials for any kind of neuro condition and infectious disease conditions. So if those are open doors for ME/CFS trials, as well as platform trials, I mean a platform that Avi brought up, that's an interesting idea. And that would require probably some more backdoor setting things up infrastructure wise. But I think that's kind of what we're doing in RECOVER with these platform trials to just try one thing after another. And people have different sets of conditions.

And you know, fatigue is in 90% of all the Long COVID cases. Post-exertional malaise is a high percent. And so we're looking at people who have really bad troubles with sleep, bad troubles with autonomic disturbances, bad exercise tolerance, and trouble with cognitive function. So those are all platforms that, you know, I think we could use for ME/CFS, and expand them, testing numerous different agents and maybe include some ME/CFS patients in those groups as well who don't have Long COVID. Now, of course, pretty soon it's going to be very hard to know who has Long COVID versus ME/CFS from something else, given the fact that so many people have been infected with COVID. But I think, yeah, the future looks definitely brighter now, unfortunately due to this pandemic, but unfortunate for ME/CFS research.

Barbara McMakin: Okay, great. Thank you. Eileen Holderman, you have your hand raised. Go ahead and unmute your line, please.

Eileen Holderman: This is Eileen Holderman. Good afternoon. How are you?

Dr. Walter Koroshetz: We're good, Eileen. Go ahead.

Eileen Holderman: Yes. Hi. Throughout the NIH, I have a comment and then a question. Throughout the NIH intramural protocol, advocates raised a major protest regarding the recruiting specifically that the criteria changed six times. And we documented that and sent it to NIH. And we were concerned that they finally settled on a combination of three criteria, one which was the IOM, which there was a major protest against including fifty international ME/CFS experts who opposed not using an expert's criteria.

So my question is to Dr. Nath, why were three different, vastly different criteria used for this comprehensive test? How can you possibly define a disease if you're using three very different criteria, particularly the IOM that was very much opposed?

Dr. Avindra Nath: It's a real challenge. You know, I mean, the problem with this disease is that you don't have objective good diagnostic criteria, right? So it's not like you can go and get a blood test done and you know what you're dealing with. So you end up with these criteria. None of them are perfect. And so they're all subjective symptoms and clinical symptomatology is never going to be perfect. So use whatever you have available.

And we put together an adjudication committee of experts in ME/CFS. And we said, you know, look at all of this and tell us whether you think this patient meets these criteria. Do you think this patient has ME/CFS or not? And we got a unanimous vote and that's only when we took these patients in there. And not only that, we were very, very rigorous to make sure that we don't have some other underlying disease that can explain their symptoms. So in the end, the only way you could explain their symptoms was by ME/CFS. So if they had any other disease we did not enroll. So I think our patient population is actually very clean, probably the best study that's ever been done, and the best patients we've included. So despite a small sample size, actually we've discovered things nobody ever could before. So I think you should be more appreciative instead of critical of the patients that we've enrolled. You know, we've done the best job that was ever possibly to be done.

Barbara McMakin: Thank you. We have another question and that came into the Q and A box. I think this one is for Dr. Nath or Dr. Breen. Does long-term antibiotic therapy have any role in the management of ME/CFS?

Dr. Avindra Nath: I would think there'd be a mistake to use long-term antibiotics and I'll tell you why, because you're going to destroy the microbiome for one. The second thing is if you think that it's a viral infection, the antibiotics aren't going to help you any. You know, in fact,

the good microbes could also be killed by the antibiotics. So at least to me, it appears that that would be a mistake.

Dr. Joseph Breen: Yeah, I guess I'd have to, I don't know, there would have to be some rationale, I don't really understand. I don't understand why you would need long-term antibiotics either in that setting. There could be a reason, but I don't know what it is in the absence of more information. So I agree with what Avi just said because there are deleterious issues that can arise, not to mention resistance. Over.

Barbara McMakin: Great, thank you. This question is for Dr. Whittemore. What can be done to engage with pharma and early stage biotechs to foster an ecosystem and encourage them to include ME/CFS in their roadmaps?

Dr. Vicky Whittemore: So thank you for that question. We're already thinking in that direction. We, I actually, have recently had several conversations with different biotech companies, some of whom are or have submitted grants to our small business program. And I think that it's something we need to really move forward with in terms of help getting some of the, especially if it's a drug that's being produced, a compound being produced by a large pharma developing, that public private partnership to really move forward together to really help to make these clinical trials a reality.

Barbara McMakin: All right, thank you. Given the challenges of travel for patients, will the trials be designed in such a way that patients can participate remotely?

Dr. Vicky Whittemore: I think that will depend on the trial and I and what sort of screening needs to be done, what kind of follow up testing is being done. But I think that is an important population, those who are homebound or in bed and bed bound, that we need to really consider as we move forward. But I think some of some of the studies may be amenable to being able to participate remotely and others not. And we'll just have to consider that as we move forward with thinking about various interventions. Avi, I don't know if you want to respond to that.

Dr. Avindra Nath: I agree with you. Yeah.

Barbara McMakin: Great. Thank you. Michel. Michel Lee, I see that your hand is raised. You can go ahead and unmute and ask your question, please. Okay.

Michel Lee: Hi. So I'm so excited by the work being done on Long COVID because it's very, the findings are, very highly consistent with my own hypothesis on post-immune assault syndrome. And I do work in an overlapping area where I think you're struggling in getting the data, you know, from the ground and sort of in the grassroots and patients and clinicians area. And I'm really wondering if some of that can be overcome by more attention to, for one thing, creating more survey instruments that go into more granularity. And these are things essentially that could harness the power of the patient, so to speak, and be very useful for clinicians.

Plus from the, from the point of the good clinicians area, people, you know, patients are getting tested for things every day. If you have these subpopulations of people with ME, with Long COVID, with long Lyme, et cetera, et cetera. Some of these lab results could be then used to send, you know, and forward the work that the NIH is doing right now. You don't have any like the clinicians don't when you wouldn't even think of that, the patients wouldn't even think of that. People don't do that at the grassroots level, but I think it could really just provide so much information that could be useful. And again, I want to really emphasize this survey issue and the need to develop more comprehensive survey instruments that don't only focus on diagnostics, but also focus on a much more detailed exploration of a lot of the sort of quirky symptoms that present in these diseases. Thank you.

Dr. Walter Koroshetz: Yeah, I think that's a great point. There's a lot of medical information out there that we don't capture. And so I think we do need to build up, you know, the specialty that's seeing the patients, they're collecting the data and the sample. You know, Joe, I don't know if Joe or Vicky want to talk, anything about the samples and the clinical data that's in the consortium now? I mean, I'm sure it's only a small fraction of what's out there, but any way to describe that quickly?

Dr. Joseph Breen: Actually, I mentioned it in my remarks briefly. The Data Management Coordinating Center at RTI has a great amount of curated data from the literature, including Drs. Wallit and Nath's latest publication. So that it's, you know, available, organized and available

to the community at large. And then if that's also connected to a search function to look in a biorepository, which actually I'd ask Vicky to describe if you could?

Dr. Vicky Whittemore: Yeah, right now the biospecimens available through the biorepository, which is called searchMECFS, is from a large cohort study that was actually supported by a private foundation and the biospecimens were transferred to us along with all of the clinical data. So in that clinical data are pretty extensive records of all the medications and supplements that those individuals were taking at the time of the study. But those biospecimens and that clinical data are available for the community to utilize. In addition, we're about to, hopefully in another month or two, add both the biospecimens and clinical information from the large MCAM multi-site study that was supported by the CDC. So those were biospecimens and clinical data that was collected across five different sites. So that information will soon be available as well.

Barbara McMakin: Okay, great. Thank you all. Thank you very much to our panelists. We are at time a recording and transcript of the webinar will be posted to the NIH ME/CFS website soon. In closing today's webinar, I'd like to remind you about our listserv for updates from NIH. To be added to the listserv, please visit the NIH MECFS website, which is www.nih.gov/mecfs, and click on Join Our Listserv.

Thank you to everyone for an informative and thoughtful discussion. Have a great afternoon.

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